ably behaving in a more or less normal fashion. Better performance of the left ventricle relieved the right ventricle of an overload, and its filling pressure underwent a considerable drop. We can therefore analyse this case as follows: The left ventricle was stimulated by digitalis. The secondary effects on the right ventricle could simply be called unloading as a result of diminution of pulmonary vascular pressures resulting from improved action of the left ventricle (Fig. 6). The absence of any increased work or output from the right ventricle under digitalis is evidence of nearly normal behaviour of this chamber. It is possible, therefore, to have a hypodynamic left ventricle leading to a secondary load on the right ventricle, the ordinary *physiological* response to which is a raised diastolic tension. This increased filling pressure of the right ventricle is reflected in a rise of venous pressure. This raised systemic venous pressure is a physiological response and does not necessarily indicate any hypodynamic or failing state of the *right* ventricle.

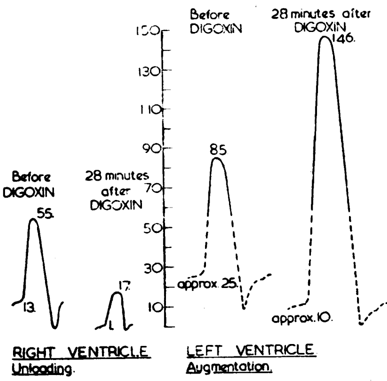

FIG. 6.—Contrasting effects of digoxin on pulse pressures of left ventricle (augmentation) and right ventricle (unloading): from data in Fig. 5. The filling pressure of the left ventricle (calculated as approximately half the pulmonary artery systolic pressure) must have fallen to a normal value.

Sometimes failure occurs with a more or less even balance of effects on the two sides of the heart. Fig. 7 is from a patient who had ischaemic heart disease probably affecting

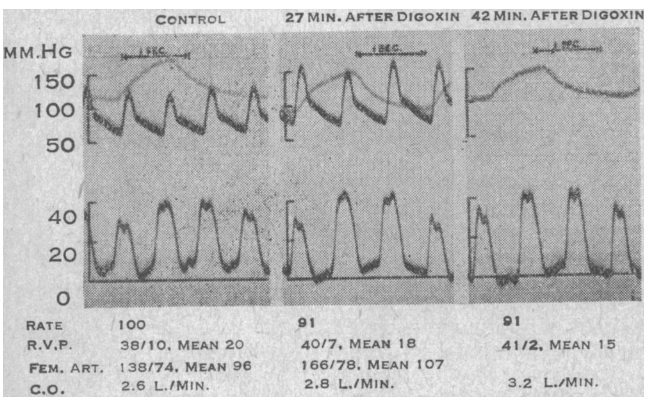

FIG. 7.—A woman aged 76 with ischaemic heart disease. A rise in arterial pressure followed digoxin, while the right ventricular pressure changed from 38/10 to 41/2 mm. Hg in 42 minutes. The cardiac output increased from 2.6 to 3.2 litres a minute. The effect of digoxin is augmentation on hypodynamic left and right ventricles.

both right and left ventricles. The right ventricle was maintaining a raised systolic pressure at the expense of some venous congestion. On digitalization the right ventricular pulse pressure rose and the diastolic filling pressure fell to a lower value; the left ventricular pressure also increased (see arterial pressure record) and the output of the heart rose significantly.

Conclusion

In this lecture I have dealt with some of the most readily analysable forms of heart failure where overload and overwork are more or less directly measurable. We have built up evidence that high venous pressure behind an overloaded chamber may be "physiological" for a time. One index of a "hypodynamic" state of the heart is probably responsiveness to digitalis. When we take into account two cardiac pumps, right and left, each in a different functional state we can begin to understand why responses to digitalis are so variable. This unpredictability of digitalis reactions seemed previously to be a bewildering maze defying rational analysis.

[The second lecture, with a list of references, will be published in our next issue.]

THE PATHOGENESIS OF SIMPLE GOITRE*

A REVIEW

BY

A. W. SPENCE, M.D., F.R.C.P.

Physician, St. Bartholomew's Hospital, London

Simple goitre is classified as a type of thyroid insufficiency. That the condition is one of importance is evidenced not only by the disfiguring nature of the disease but by the serious disorders to which it may give rise or predispose—namely, cretinism, myxoedema, and carcinoma of the thyroid gland. Cancer of the thyroid gland is comparatively rare in Britain, but in Switzerland, where simple goitre is common, the deaths from carcinoma of the thyroid gland formed 1.6% of the total deaths from cancer in the years 1901 to 1910 and 0.98% in the period 1911 to 1920 (Renaud, 1923). According to Bérard and Dunet (1924), in 75 to 85% of cases thyroid malignancy develops in an old-standing simple goitre.

Pathology

Before the pathogenesis of simple goitre is discussed reference should be made to its pathology, for it should be appreciated that simple hyperplastic goitre, colloid goitre, and nodular goitre are all stages of the same disease process and are not separate entities with their own particular aetiology. Nodular goitre was once believed to be a different disease from diffuse goitre, and colloid goitre was thought to be due to overactivity of the colloid storage mechanism whereby the normal gland was converted straightaway into a colloid goitre without any intervening stage of hyperplasia. We now know through the work of Marine, although Virchow (1863a) originally pointed it out, that the primary phase of all true goitres is active hyperplasia, and that the development of a colloid goitre from a normal gland by the passive distension of the follicles with colloid is impossible.

Marine and Lenhart (1909a) showed that thyroid hyperplasia is associated with a decrease of the iodine store of the gland. The morphologically normal thyroid gland contains on an average about 0.2% of iodine (measured in terms of dried gland). When the requirements of the organism for thyroid hormone increase the iodine store of the thyroid diminishes, and when it falls below 0.1% the gland is found to be hyperplastic. These changes are brought about by stimulation by the anterior pituitary thyrotrophic hormone, the secretion of which is increased as a result of a fall in the blood level of thyroid hormone.

*Presidential address (abridged) delivered to the Section of Endocrinology, Royal Society of Medicine, on January 23, 1952.

Genesis of Colloid Goïtre.—If the stimulus persists for long enough the gland becomes enlarged as a result of the hyperplasia. If the stimulus then subsides, or if iodine is given, the thyroid will involute to the colloid phase. Because of the previous increase in the number of cells in each follicle the follicles will be larger than those of the normal gland, and because of the greatly increased volume of glandular tissue, now no longer necessary, there will be passive distension of the follicles with colloid. Thus is a colloid goitre produced. Through alternating hyperplasia and involution large colloid goitres are formed and active hyperplasia may be present in a colloid goitre, the colloid material of which in such a case is poor in iodine.

Genesis of Nodular Goitre.—The benign nodules which may occur in the thyroid gland are (1) those which are fully differentiated and are of the hyperplastic or colloid type, and (2) those which are incompletely differentiated—namely, the trabecular, tubular, and microfollicular adenomas. (These thyroid nodules are not true adenomas in the pathological sense, but they *may* be potential tumours.) The formation of benign nodules is intimately bound up with the genesis of simple goitre, the stimulus for the production of nodules is the same as for the production of diffuse goitre, and nodules do not occur in glands which are not, or have not been, hyperplastic.

The work of Rienhoff (1931) has shown that the fully differentiated nodules usually arise through the repeated and alternating processes of hyperplasia and involution. In the human thyroid gland involution proceeds irregularly; portions of the gland may show hyperinvolution with the formation of follicles distended with colloid, whereas other portions remain as islands of hyperplasia. Repeated hyperplasia and involution bring about increase of stroma and endarteritis; these changes lead to differences in blood supply whereby colloid-retention cysts are formed. Between the cysts there may be islands to which the blood supply is unimpaired and which therefore may become hyperplastic. By continued growth these hyperplastic areas enlarge and assume a false capsule by compressing adjacent thyroid tissue. The enlargement of these areas is not necessarily due to any biological abnormality of the cells, but to the fact that a large amount of glandular tissue in the form of colloid retention cysts is, as it were, out of action.

The undifferentiated nodules are formed through a process of budding from thyroid epithelium. The thyroid gland must first of all become hyperplastic; eventually in places degeneration due to exhaustion occurs and a compensatory and regenerative epithelial proliferation takes place in another part of the lobule. Sometimes mature follicles are not formed, and thus arise nodules in various stages of differentiation—the trabecular, tubular, and microfollicular adenomas. In this case there must be some biological abnormality of the cells; it is probably an exhaustion phenomenon following the prolonged stimulation (Virchow, 1863b; Hitzig, 1894; Michaud, 1906; Wegelin, 1932, personal communication).

The longer the individual has had a goitre the more likely is the goitre to be colloid than one of simple hyperplasia, and long-standing goitres are more likely to be nodular. A congenital goitre in an infant is almost always hyperplastic because it has not had the chance to involute. According to Wegelin (1932, personal communication), nodules are rarely found in the thyroid gland of an individual under the age of 10 years because they have not had time to form. It is very doubtful, therefore, whether congenital adenomas exist.

Pathogenesis

Iodine was first used with success in the treatment of goitre by Coindet (1820), and Prévost (1830) first suggested that the cause of endemic goitre might be a deficiency of iodine in the water supply. Chatin (1852) conducted an iodine survey in the Alps, where goitre is prevalent, and found that the soil, water, and foodstuffs were low in iodine. The presence of iodine in the thyroid gland was not demonstrated until 1895, a discovery which was made by Baumann. Although the early observations suggested a definite relationship between goitre and iodine deficiency, they were subjected to a good deal of criticism, and, the iodine theory not being generally accepted, a large number of hypotheses were put forward concerning the causation of goitre. To most of these I shall make no reference, but will discuss the experimental work that has been carried out in modern times on the pathogenesis of simple goitre.

Iodine Deficiency

It has been established that iodine deficiency gives rise to goitre. The converse, however, that all simple goitres are due to iodine deficiency—that is, a deficient intake—is not true. The evidence that goitre is caused by iodine deficiency is as follows: (1) iodine surveys have shown that endemic goitre is related to a deficiency of iodine in the soil, water, and foodstuffs growing in that region; (2) the urinary excretion of iodine has been shown to be much diminished in persons living in a district with a high incidence of goitre; (3) the administration of iodine to persons living in endemic areas reduces the incidence of goitre; (4) the incidence of goitre on the seacoast is low owing to the high consumption of sea food rich in iodine; (5) hyperplastic goitre may be produced in animals by means of iodine-poor diets; and (6) the percentage of iodine in hyperplastic goitres is low and varies inversely with the degree of hyperplasia.

As a result of iodine deficiency the secretion of thyroid hormone, the active principle of which—thyroxine—contains four atoms of iodine, is reduced, and this brings about increased secretion of thyrotrophin by the anterior pituitary gland which causes hyperplasia and enlargement of the thyroid gland.

Congenital Goitre

If the deficient intake of iodine is prolonged exhaustion atrophy of the thyroid cells ultimately takes place and hypothyroidism develops. Pregnancy throws an added strain on the maternal thyroid gland—that is, the demands of the body for thyroid hormone are increased. If the goitrous thyroid of the mother is able to meet these demands and maintain the normal level of thyroid hormone in the blood stream, goitre in the foetus will not develop, but if the maternal thyroid gland is unable to do this, through exhaustion of its cells, congenital goitre in the offspring will result. It is well known, through the original experiments of Halsted (1896), that congenital goitre may be produced in animals by removing most of the mother's thyroid gland during early pregnancy; and Marine and Lenhart (1909b) showed that congenital goitre could easily be prevented in such experiments by giving the mother iodine during her pregnancy.

While a deficient intake of iodine explains the high incidence of goitre in certain endemic regions, it is not the common factor in the production of all goitres. It is obviously not the cause of sporadic goitre, which occurs in a city like London, where there is no iodine deficiency. McCarrison and his colleagues (1927) could find no evidence in Himalayan India that the incidence of endemic goitre bore any relation to the iodine content of the soil and drinking water. Further, many of the inhabitants of Switzerland, where it has been definitely shown that the soil, water, and foodstuffs grown are deficient in iodine, have colloid goitres, which means that the iodine intake of these persons is high enough to enable the thyroid gland, which was previously hyperplastic, to involute and remain in the passive colloid phase. There must therefore be some other factor responsible for the production of thyroid hyperplasia, and the Swiss authorities themselves do not believe that a deficient intake of iodine is the only factor which accounts for goitre in Switzerland.

Let us consider the colloid goitres of the Swiss natives. It is well known that during the periods of growth, puberty, and pregnancy the requirements of the individual for thyroid hormone are greater than at other periods of life, and that in the experimental field goitre can be produced more easily in the young growing animal than in the adult. Not all Swiss natives have visible goitres, although most of them are probably taking similar food; hence the deficiency of iodine in the diet may not be severe enough to give rise by itself to any marked thyroid enlargement and the potency of the second or X factor, whatever it may be, varies in different persons. During those periods when the organism's requirements of thyroid hormone are increased—that is, when the X factor is acting—the amount of ingested iodine in the endemic region is far from adequate and there results in a large percentage of the population a hyperplastic goitre. When the individual's requirements of thyroid hormone later diminish—that is, when the X factor wanes—the amount of iodine ingested is sufficient for this lower level of thyroid activity, and the gland involutes to the colloid or resting phase. In regions where there is no endemic goitre the amount of ingested iodine is enough in most cases to tide the gland over these periods of increased need of the hormone. We shall have to consider later what this other factor may be.

Infection and Diet

The second hypothesis that must be mentioned is that of infection. McCarrison (1917) was the great protagonist of the toxaemic theory. As a result of his investigations in the Ganges basin he concluded that intestinal toxaemia was an important cause of goitre and that the organisms responsible were conveyed to man and animals by infected food and water. The opinions of McCarrison, who spent a lifetime on goitre research in India, must be treated with respect, but I think it may be said with some certainty that there is no evidence that toxaemia is a cause of goitre in the Western world. It is well known that infections of any type increase the activity of the thyroid gland and that they may cause temporary thyroid enlargement in persons with a minimal supply of iodine adequate for normal requirements or in persons subjected to other influences favourable to the genesis of goitre, but in most individuals with endemic and sporadic goitre in Europe and America there is no evidence of infection.

Apart from diets deficient in iodine, it is doubtful what part diet plays in the causation of goitre. It is known that a high intake of fat or of meat protein may cause thyroid hyperplasia in laboratory animals, but it is questionable whether this finding has any real clinical significance. Unbalanced diets may be contributory factors, and there is evidence that excessive ingestion of foods containing goitrogenic substances may be responsible for a high incidence of goitre in certain regions. Before embarking on this aspect of the question I shall discuss certain specific substances that have been inculpated.

Calcium and Fluorine

Répin (1911) seems to have been the first investigator to suggest that an excess of calcium in the water may be an aetiological factor in the production of goitre. It has been said that the high calcium content of the waters of Derbyshire is responsible for "Derbyshire neck." This is not the only goitrous area in which the calcium content of the water is high, but, on the other hand, there are many areas where the calcium content is high without goitre and other areas where the calcium content is low with goitre, indicating that calcium is not an essential factor (Marine, 1935). It has been shown experimentally that a high calcium intake enhances the goitrogenic effect of a low iodine diet (Hellwig, 1931; Thompson, 1933). It is not understood how an excessive intake of calcium favours the production of goitre; it has been suggested that calcium binds iodine in such a manner as to interfere with its absorption from the gut. Raising the iodine intake neutralizes the effect of a high calcium diet (Thompson, 1933).

The suggestion has been made that excess of fluorine in the drinking-water may be a contributory factor in endemic goitre, and from several parts of the world there have been reports of the coexistence of fluorosis and endemic goitre. Wilson (1941) reported a high degree of dental fluorosis (mottled enamel) in the goitrous areas of the Punjab and a certain parallelism between the incidence of goitre and dental fluorosis in Somerset. On the other hand, endemic goitre has not been reported from the fluorosis areas in the United States of America, and the incidence of goitre may be high in areas in which the fluorine intake is either high or low (Murray *et al.*, 1948).

Vitamin Deficiency

The question of the part played by vitamin deficiency in the aetiology of simple goitre has occupied the attention of a number of investigators. McCarrison and Madhava (1932) found thyroid enlargement in a considerable percentage of their animals fed on a diet deficient in all vitamins. Spence (1932), using one of McCarrison's diets deficient in all vitamins but containing an adequate amount of potassium iodide, obtained thyroid enlargement in 75% of his animals. They showed keratinization of the thyroid epithelium due to vitamin-A deficiency, and most of the glands were moderately hyperplastic. It is possible that the thyroid enlarges under these conditions because much of the epithelium is either keratinized or damaged and a compensatory hypertrophy takes place.

Sandberg and Holly (1933) induced thyroid hyperplasia in rabbits with a vitamin-B-deficient diet, but the addition of vitamin B did not bring about involution. Several investigators have observed enlargement and pronounced hyperplasia of the thyroid gland of rats fed on a rachitogenic diet. Thompson (1932) observed thyroid hyperplasia in a high percentage of rats receiving modifications of Steenbock's rachitogenic diet with or without the addition of vitamin D. From these experiments, therefore, it cannot be concluded that the hyperplasia was due to vitamin-D deficiency; an iodine deficiency is difficult to exclude—in fact, in all experiments dealing with the production of goitre by vitamin deficiency it is often difficult to exclude an iodine deficiency as the cause of the goitre unless an adequate, though minimal, amount of iodine is added to the diet.

On the whole the experimental work is contradictory and controversial, and in the clinical field there is no evidence that vitamin deficiency plays a primary part in the aetiology of endemic or sporadic goitre, although it may be a contributory factor.

"Cabbage Goitre"

Chesney *et al.* (1928) discovered accidentally that their stock rabbits, maintained on a diet consisting of a daily ration of fresh cabbage, a ration of oats three times a week, and one of hay once a week, developed large hyperplastic goitres. This observation was the inception of the discovery of the antithyroid effect of thiouracil. The production of goitre in rabbits by cabbage feeding was confirmed by Marine *et al.* (1929) in New York, by McCarrison (1931) in India, and by Spence *et al.* (1933) in England. There is abundant evidence to show that cabbage goitre is caused, not by a deficient intake of iodine, but by a positive goitrogenic agent. Marine *et al.* (1929) soon observed that other vegetables of the *Brassica* group, to which cabbage belongs, were goitrogenic—namely, brussels sprouts, cauliflower, kohlrabi, rutabaga (swede), and turnip. Some years later Hercus and Purves (1936) discovered that the seeds of certain brassicae, notably rape seed, mustard seed, and cabbage seed, caused goitre when fed to rats.

Nature of the Goitrogenic Substance

It was obviously important to determine the nature of the goitrogenic substance. Because organic cyanides are present in several of the Cruciferae, the botanical name of the group of vegetables mentioned above, and because cyanides are powerful depressors of tissue oxidation, Marine *et al.* (1932) tried the effect of small doses of organic cyanides, the hypothesis at that time being that the goitrogenic agent acts by depressing some oxidation system, an effect which the thyroid gland attempts to overcome by producing a larger amount of its hormone, with consequent hyperplasia. These experiments met with success, and the greatest thyroid response was obtained with methyl cyanide (acetonitrile), which produced in rabbits striking hyperplasia in three weeks, the glands of the control animals being normal. It was concluded, therefore, that the goitrogenic substance in cabbage was an organic cyanide.

When organic cyanides are administered they are broken down in the body to hydrocyanic acid, part of which is neutralized by sulphur and excreted as thiocyanate. The goitrogenic property of methyl cyanide could therefore be due either to the gradual liberation of hydrocyanic acid or to the detoxication product, thiocyanate. To determine whether thiocyanate was responsible we investigated the action of sodium thiocyanate. Given subcutaneously to rabbits in doses of 0.025 to 0.2 g. daily for three weeks, it had an entirely negative effect (Marine *et al.*, 1932). It was therefore concluded that the substance responsible was hydrocyanic acid, which had to be liberated gradually in order to produce a continuous action, that treatment with an inorganic cyanide, such as potassium cyanide, was ineffective because its action was short-lived, and that a relatively stable compound, such as phenyl cyanide, was ineffective because little hydrocyanic acid was liberated. (It is of interest that we obtained negative results with sodium thiocyanate, because it is now known that this substance is goitrogenic. The experiment may not have been continued for long enough, or the rabbit may deal with the compound in a manner different from the human or the rat, in which animal thiocyanate goitre has been produced more recently in ten days.)

Since these experiments several investigators have been unable to confirm the goitrogenic action of methyl cyanide. Strangely enough, one of the first of these was myself, working with Dr. E. F. Scowen at St. Bartholomew's Hospital on my return from Marine's laboratory in New York. In 1934 I wrote: "Having had practical experience of the production of thyroid hyperplasia by means of cyanide, we cannot deny its goitrogenic power; but it appears that the conditions for its production, whatever they may be, must be adjusted to a nicety before its effect is visible. From these observations we can be fairly safe in concluding that it is extremely doubtful whether cyanide is the substance in cabbage responsible for the production of goitre." Yet in Marine's laboratory we obtained in a rabbit treated with methyl cyanide for seven months a goitre weighing 2.415 g., whereas the gland of the control animal of approximately the same weight and kept under identical conditions weighed 0.167 g.

Richter and Clisby (1941) observed that phenylthiourea produced thyroid enlargement in rats. Kennedy (1942) then showed that allylthiourea was goitrogenic and suggested that it might be the active substance in cabbage, but he did not state how he arrived at this conclusion. Since then a number of goitrogenic compounds have been discovered, including the sulphonamides, potassium thiocyanate, thiouracil, and other derivatives of thiourea, but no goitrogenic substance was isolated from any of the vegetables and seeds capable of producing goitre until Astwood *et al.* (1949) isolated the goitrogen *l*-5-vinyl-2-thio-oxazolidone from rutabaga and from brassica seeds. As in goitre caused by iodine deficiency, the anterior pituitary thyrotrophic hormone is directly responsible for the thyroid changes, for thyroid enlargement cannot be produced by means of brassica seeds or antithyroid compounds in hypophysectomized animals.

It is doubtful what bearing, if any, these goitrogenic compounds have in the spontaneous development of goitre in man. Greer *et al.* (1949) have attempted to correlate the pathogenesis of certain cases of human goitre with a high intake of goitrogenic vegetables. They mentioned two patients of Professor Means who developed goitres when their diet consisted of large amounts of cabbage. When the cabbage was omitted the gland became smaller, but it enlarged again when the cabbage diet was resumed. The incidence of goitre in Holland and Belgium increased during the recent war, when the diet consisted largely of cabbage, turnip, and similar foods. Although a large number of people exist on vegetarian diets and do not appear to have goitres, Greer and his colleagues suggested that it is worth keeping in mind that sporadic goitre may occasionally be due to the ingestion of goitrogenic foods.

Antigoitrogenic Substances Other than Iodine

Reference should be made to the possible existence of antigoitrogenic substances other than iodine, a deficiency of which in the diet may play a part in the genesis of simple goitre. Marine and his colleagues (1933) showed that the development of "cabbage goitre" can be prevented by the feeding of certain fresh plants. They produced evidence that the antigoitrogenic action of these plants is not likely to be due to iodine. Variations in the goitrogenic potency of cabbage and similar vegetables may be due not only to variations in the content of the goitrogenic factor but also of an antigoitrogenic substance.

Endogenous Disturbances

So far I have dealt only with exogenous factors, which are probably more applicable to the pathogenesis of endemic goitre than of sporadic goitre, since they are more likely to affect a whole community than isolated individuals. The X factor for which we are searching and which is at present unknown will probably prove to be some endogenous disturbance. This hypothesis is suggested by the observations that the environmental factors, the diet, and the conditions of life of individuals with sporadic goitre are in the main no different from those of non-goitrous persons, that goitre is commoner in females than in males, and that it is prone to arise at certain periods of life—namely, puberty, pregnancy, and the menopause. The frequent occurrence of goitre at these sex periods suggests an interrelationship between the thyroid gland and the gonads, but the nature of this relationship is uncertain and the experimental work controversial; some observers have found decreased thyroid activity after gonadectomy, and others have repeatedly found thyroid hyperplasia (Aron and Benoit, 1931; Loeser, 1935).

It is possible that the endogenous disturbance may be connected with tissue oxidations, or there may be normally present in the body substances with antigoitrogenic and goitrogenic properties, a well-known example of the latter being thiocyanate in the saliva. Variations in the production of these substances may be responsible for enlargement of the thyroid gland.

Summary

It is believed that a deficient intake of iodine is the fundamental cause of goitre in most endemic areas, and that abnormalities of diet and unhygienic living conditions are probably contributory factors. Abnormalities of diet may consist in excess of calcium, vitamin deficiency, excess of goitrogenic vegetables, or a deficiency of some antigoitrogenic substance other than iodine.

Sporadic goitre is caused by an endogenous disturbance, which also plays a part in the genesis of endemic goitre; the nature of the disturbance is unknown.

REFERENCES

Aron, M., and Benoit, J. (1931). *C.R. Soc. Biol., Paris*, **108**, 784.
Astwood, E. B., Greer, M. A., and Ettlinger, M. G. (1949). *J. biol. Chem.*, **181**, 121.
Baumann, E. (1895). *Hoppe-Seyl. Z.*, **21**, 319.
Bérard, L., and Dunet, C (1924). *Le Cancer Thyroïdien*. Doin, Paris.
Chatin, A. (1852). *Gaz. Hôp., Paris*, **25**, 14, 38, 50, 82, 86, 94.
Chesney, A. M., Clawson, T. A., and Webster, B. (1928). *Bull. Johns Hopk. Hosp.*, **43**, 261.
Coindet, J. R. (1820). *Ann. Chim. Phys.*, **15**, 49.
Greer, M. A., Ettlinger, M. G., and Astwood, E. B. (1949). *J. clin. Endocr.*, **9**, 1069.
Halsted, W. S. (1896). *Johns Hopk. Hosp. Rep.*, **1**, 373.
Hellwig, C. A. (1931). *Arch. Path.*, **11**, 709.
Hercus, C. E., and Purves, H. D. (1936). *J. Hyg., Camb.*, **36**, 182.
Hitzig, Th. (1894). *Arch. klin. Chir.*, **47**, 464.
Kennedy, T. H. (1942). *Nature*, **150**, 233.
Loeser, A. (1935). *Klin. Wschr.*, **14**, 4.
McCarrison, R. (1917). *The Thyroid Gland*. Baillière, Tindall and Cox, London.
—— (1931). *Indian J. med. Res.*, **18**, 1311.
—— and Madhava, K. B. (1932). Indian med. Res. Mem. No. 23. Thacker, Spink and Co., Calcutta.
—— Newcombe, C., Viswanath, B., and Norris, R. V. (1927). *Indian J. med. Res.*, **15**, 207.
Marine, D. (1935). *J. Amer. med. Ass.*, **104**, 2334.
—— Baumann, E. J., and Cipra, A. (1929). *Proc. Soc. exp. Biol., N.Y.*, **26**, 822.
—— —— Spence, A. W., and Cipra, A. (1932). Ibid., **29**, 772.
—— —— Webster, B., and Cipra, A. (1933). *J. exp. Med.*, **57**, 121.
—— and Lenhart, C. H. (1909a). *Arch. intern. Med.*, **3**, 66; **4**, 440.
—— —— (1909b). Ibid., **4**, 253.
Michaud, L. (1906). *Virchows Arch.*, **186**, 422.
Murray, M. M., Ryle, J. A., Simpson, B. W., and Wilson, D. C. (1948). Med. Res. Coun. Mem. No. 18. H.M.S.O., London.
Prévost (1830). Quoted by St. Lager (1867).
Renaud, A. (1923). *Rev. méd. Suisse rom.*, **43**, 433.
Répin, Ch. (1911). *C.R. Soc. Biol., Paris*, **71**, 225.
Richter, C. P., and Clisby, K. H. (1941). *Proc. Soc. exp. Biol., N.Y.*, **48**, 684.
Rienhoff, W. F., jun. (1931). *Medicine*, **10**, 257.
St. Lager, J. (1867). *Etudes sur les Causes du Crétinisme et du Goître Endémique*, p. 239. Baillière, Paris.
Sandberg, M., and Holly, O. M. (1933). *J. biol. Chem.*, **99**, 547.
Spence, A. W. (1932) *Brit. J. exp. Path.*, **13**, 157.
—— (1934). *St. Bart's Hosp. Rep.*, **67**, 203.
—— Walker, F. H. A., and Scowen, E. F. (1933). *Biochem. J.*, **27**, 1992.
Thompson, J. (1932). *J. Nutr.*, **5**, 359.
—— (1933). *Arch. Path.*, **16**, 211.
Virchow, R. (1863a). *Die krankhaften Geschwülste*, **3**, 4. Berlin.
—— (1863b). Ibid., **3**, 15.
Wilson, D. C. (1941). *Lancet*, **1**, 211.

ACUTE CIRCULATORY FAILURE DURING SURGICAL OPERATIONS

BY

J. F. DARK, M.B., Ch.B., B.Sc., F.R.C.S.

T. DINSDALE, M.B., Ch.B., D.A.

A. N. GUTHKELCH, M.Ch., F.R.C.S.

AND

L. P. LASSMAN, M.B., B.S., F.R.C.S.

(From the Thoracic Surgical Centre, Manchester Region, and the Royal Manchester Children's Hospital)

For as long as surgery has been practised deaths have occurred during operation. Presumably most of these were at first due to shock and loss of blood, though it is said that Greek surgeons sometimes gave their patients narcotic drugs to diminish pain, and that on occasion these drugs themselves caused death.

The first anaesthetic death in the modern sense, however, occurred in Newcastle-upon-Tyne on January 28, 1848 : it was due to the use of chloroform (Beecher, 1941). A similar case occurred in Manchester four years later (Anon., 1853). By 1874 experimental cardiac massage had restored the heart beats in dogs anaesthetized with chloroform, and the first human life was saved in this way in 1902. A review of the results (Barber and Madden, 1945) of cardiac massage showed that in 1906 there were 22.5% complete recoveries, while for the years 1924–45 the reported success rate had risen to 52%. It is, of course, unlikely that the real expectation of survival is as high as this, as a single success is more likely to appear in the literature than a single failure.

The causes of sudden heart failure in the operating theatre have already been reviewed (Ruzicka and Nicholson, 1947 ; Lahey and Ruzicka, 1950). For our purposes it is sufficient to recognize that they fall into three main groups : (1) those due to or associated with pre-existing disease, usually the disease for the relief of which operation is being performed ; (2) those resulting from what may be termed the immediate general complications of surgery, notably shock, haemorrhage, and air embolism ; and (3) those due to the anaesthetic agent or technique.

Group 1

In these cases the only possible treatment is to try to undo the damage as quickly as possible. If cardiac massage is used at all (as in Case 2) it is only incidentally.

Case 1: Cardiac and respiratory failure due to acute medullary compression; attempted relief of compression and cardiac massage; death.—A 3-months-old girl was about to undergo the excision of an occipital encephalocele. After a normal induction of anaesthesia with intubation her head was for a moment allowed to rest directly on the encephalocele. There was an immediate slowing of respiration, which recovered in a few minutes. She was then turned on to her face for the operation, and immediately the respiration slowed again, both it and the pulse failing completely within a few minutes. Immediate aspiration of cerebrospinal fluid from the encephalocele, intracardiac injection of procaine-adrenaline solution, and, finally, cardiac massage were unsuccessful. At necropsy there was found to be a gross malformation of the hind-brain (Arnold–Chiari malformation); abnormally long cerebellar tonsils had prolapsed through the foramen magnum and given rise to strangulation of the medulla oblongata, hence the respiratory and cardiac arrest. Such a case cannot be saved by any normal resuscitative measure.

Case 2: Asphyxia, with cardiac failure, due to respiratory obstruction; relief of obstruction; artificial respiration and cardiac massage; temporary recovery.—A middle-aged woman was admitted to hospital in the last stages of asphyxia due to haemorrhage into a thyroid cyst. She was rushed to an operating theatre, but as she was laid upon the table her heart stopped. A stiff intratracheal tube was rapidly inserted, the lungs were inflated with oxygen, and within another two minutes cardiac massage was begun. The heart and respiration restarted, and it was then possible to deliver and remove the thyroid swelling, some local analgesic being used in the later stages of the operation. When the intratracheal tube was removed the patient was actually able to thank the surgeon for saving her life, but she went into coma some 12 hours later and died within two days. At necropsy there were found to be multiple petechial haemorrhages throughout the brain. The appearances were characteristic of those seen in patients who have undergone long periods of asphyxia. It is of interest to recall that in certain cases of carbon monoxide poisoning there may also be temporary recovery of consciousness followed by coma and death, with similar post-mortem appearances.

Group 2

Cardiac massage has of course little or no part to play in resuscitation from shock and haemorrhage. We have used it unsuccessfully in one case of air embolism. This case is unusual enough to merit a brief report.

Case 3: Air embolism resulting from air encephalography; cardiac massage; death.—A boy aged 2 years was undergoing air encephalography by the lumbar route under bromethol narcosis with a little ethyl chloride to maintain relaxation. He had been knocked down by a lorry one month before and had since been subject to attacks of vomiting and what might have been minor epileptic fits. The air encephalogram was regarded as desirable to clear up the diagnosis, since there were no signs of increased intracranial pressure. Just as a 30-ml. replacement of cerebrospinal fluid by air was completed the patient became cyanosed, with sighing respiration. Thereafter the pulse failed completely. Four minutes later, forced insufflation of oxygen having failed to improve him, a left paramedian abdominal incision was made and the heart palpated. It was found to be flaccid, but after a